

## PATENT SPECIFICATION

NO DRAWINGS

973,361



Date of Application and filing Complete Specification: May 10, 1961.

No. 17103/61.

Application made in Switzerland (No. 5403) on May 11, 1960.

Application made in Switzerland (No. 3929) on April 4, 1961.

Complete Specification Published: Oct. 28, 1964.

© Crown Copyright 1964.

Index at acceptance:—C2 C(1E6K4, 1Q6C, 1Q7A, 1Q8A, 1Q9C, 1Q9B, 1Q11G, 2B4A4, 2B4F, 2B4G5, 2B4G6, 2B4G10, 3A12A4A, 3A12B1, 3A12C6, 3A14A3A, 3A14A7C)

International Classification:—C 07 d

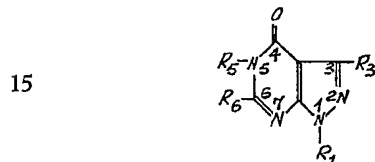
## COMPLETE SPECIFICATION

## Pyrazolo-Pyrimidines and process for their manufacture

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new pyrazolo-pyrimidines, a process for their manufacture and pharmaceutical preparations containing them.

The present invention provides pyrazolo-[3,4-d]-pyrimidines of the formula



and quaternary ammonium compounds or salts thereof. In the above formula  $R_1$  represents a hydrogen atom or an alkyl, hydroxy-alkyl or oxa-alkyl group, or a cycloalkyl group, or an at most binuclear aryl group or a pyridyl group.  $R_1$  may represent, for example, a lower alkyl group such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl-(1), pentyl-(2), pentyl-(3)-, 2-methyl-butyl-(3)- or hexyl group, a 3-oxa-pentyl or 5-oxa-heptyl-(2) group, or a hydroxy-lower-alkyl group, such as a hydroxyethyl group, a cyclopentyl or cyclohexyl group, or a phenyl group, in which the aromatic nuclei may be substituted, for example, by lower alkyl or free or substituted hydroxy groups, halogen atoms or trifluoromethyl groups, or a pyridyl group. The aforesaid substituted hydroxy groups may contain substituents of the kind referred to above, and especially lower alkyl groups,

for example, methoxy, ethoxy, propoxy or butoxy groups or alkylene-dioxy, such as methylene-dioxy, groups. As halogen atoms there may be mentioned, more especially, fluorine, chlorine, or bromine.

$R_2$  represents a lower alkyl group, for example one of those mentioned for  $R_1$ , especially methyl, but  $R_2$  preferably represents a hydrogen atom.

$R_3$  represents a lower branched or straight chained alkyl group bound in any position, such as a methyl, ethyl, propyl, isopropyl, butyl, pentyl-(1), pentyl-(2), pentyl-(3), 2-methyl-butyl-(3)- or hexyl group; or more especially a tertiary aminoalkyl group, for example, one in which the amino group is disubstituted by lower alkyl groups or a lower alkylene group, the carbon chain of which may be interrupted by oxygen, sulphur or nitrogen. There may be mentioned, more especially, dimethylamino-, diethylamino-, pyrrolidino-, piperidino-, morpholino-, piperazino-, N-methyl-piperazino-ethyl-, -propyl or -butyl groups.

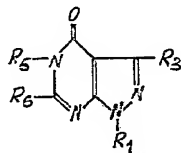
$R_4$  represents an alkyl group or an aralkyl group which may be substituted.  $R_4$  may be, for example, a lower alkyl group, such as a methyl or ethyl group or a group containing more than two carbon atoms, such as a propyl, isopropyl, butyl, isobutyl, pentyl-(1), pentyl-(2), pentyl-(3), 2-methyl-butyl-(3) or hexyl group, but especially a phenyl-alkyl, such as a phenyl-lower alkyl, for example 1- or 2-phenyl-ethyl, 1-phenyl-propyl or phenyl-methyl group, in which the aromatic nucleus may contain substituents, such as lower alkyl or free or substituted hydroxy, amino or mercapto groups, halogen atoms or trifluoromethyl or nitro groups. The alkyl groups are, for example, methyl, ethyl, propyl or butyl and may be substituted, for example, by a further aryl group, as in the case of the diphenyl-methyl group. Substituted

hydroxy, mercapto or amino groups bound to the phenyl groups are above all lower alkoxy groups, such as methoxy, ethoxy, propoxy, butoxy, methylene-dioxy, methylmercapto or dimethylamino groups. As halogen atoms there may be mentioned above all chlorine and bromine.

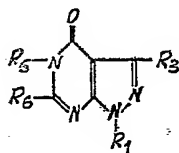
The term "lower" in qualifying the hydrocarbon groups is used herein to mean those groups containing up to 7 carbon atoms.

The new compounds of this invention possess valuable pharmacological properties, and they possess more especially a coronary dilating action. The new compounds are, therefore, useful as medicaments, more especially in circulatory disturbances in the myocardium, and they are useful as intermediate products for making such medicaments.

Especially valuable as coronary dilating agents are compounds of the formula

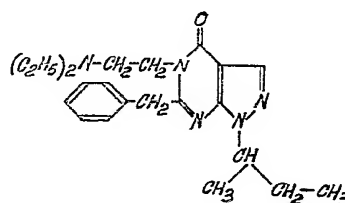


and salts thereof, in which formula  $R_1$  represents a hydrogen atom or a lower alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl-(2), 3-methyl-butyl-(2), pentyl-(2) or pentyl-(3); or a cycloalkyl group such as cyclopentyl or cyclohexyl, an hydroxy-lower-alkyl group, such as hydroxyethyl, an oxalower-alkyl such as 3-oxapentyl group; or an aryl group, such as a phenyl group in which the aryl group may be unsubstituted or mono-, di- or tri-substituted by halogen, such as chlorine or bromine, an alkoxy such as methoxy, or ethoxy, alkyl such as a methyl, ethyl, propyl, isopropyl, butyl, tertiary-butyl or methylene-dioxy, or trifluoromethyl, or a pyridyl group;  $R_2$  represents a hydrogen atom or a lower alkyl group;  $R_3$  represents a lower alkyl-group, for example, one of those mentioned above, or a tertiary-amino-lower alkyl group, especially one of those mentioned above; and  $R_4$  represents a lower alkyl group, for example one of those mentioned above or an aralkyl group, such as a phenyl-alkyl, especially a phenylmethyl, group in which the aryl group may be substituted in the manner indicated above. Especially valuable are compounds of the formula



and salts thereof, in which formula  $R_1$  represents a hydrogen atom or preferably a lower alkyl group, especially a branched alkyl group, such as an isopropyl or secondary-butyl group,  $R_2$  represents a lower alkyl group or preferably a hydrogen atom,  $R_3$  represents a dilower-alkylamino-, pyrrolidino-, piperidino-, morpholino- or piperazino-lower-alkyl group, and especially a dimethylamino- or diethylamino-ethyl or propyl group, and  $R_4$  represents an unsubstituted or mono-, di- or trisubstituted benzyl group substituted in the phenyl group by chlorine, methoxy, methylene-dioxy, methyl or trifluoromethyl.

Especially valuable is 1-secondary-butyl-5-( $\beta$ -diethyl-aminoethyl)-6-benzyl-4-hydroxy-4:5-dihydro-pyrazolo-(3,4-d)-pyrimidine of the formula



and salts thereof.

The invention also provides a process for the manufacture of the above new compounds, wherein the tautomerisable hydrogen atom present in a 1- $R_1$ -3- $R_2$ -4-oxo-4:5-dihydro-6- $R_3$ -pyrazolo-[3,4-d]-pyrimidine is exchanged by a method in itself known for the radical  $R_4$ , the symbols  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  having the meaning given above. Preferably this is brought about by treating the pyrimidine compound with a reactive ester of an alcohol of the formula  $R_4OH$ . As reactive esters there may be mentioned those of strong inorganic or organic acids, for example, hydrohalic acids, sulphuric acid or organic sulphuric acids, for example, aryl sulphonic acids such as toluene sulphonic acids, and as alcohols there may be mentioned more especially lower alkanols or amino-alkanols substituted, for example, in the manner indicated above. The reaction is carried out in the usual manner, in the presence of a basic condensing agent, such as an alkali metal hydroxide, alcoholate, hydride or amide.

The tertiary amines so obtained can be quaternated in the usual manner, for example, with reactive esters of alcohols, such as alkanols or phenyl-alkanols. In the compounds so obtained substituents may be introduced or exchanged. Thus, for example, aryl radicals may be nitrated, and nitro-aryl radicals reduced in the usual manner to amino-aryl radicals, or hydroxy alkyl or halogen-alkyl

radicals, for example, in the 5-position, may be converted in a known manner into amino-alkyl or ammonium-alkyl radicals. The hydroxy-alkyl and halogen-alkyl radicals may be converted, for example, in the usual manner by reacting a hydroxy-alkyl or halogen-alkyl group, in the case of a hydroxy-alkyl group after converting it into a reactive ester, with ammonia or an amine.

The products so obtained of basic character form salts with inorganic or organic acids. As acid forming salts there are used, therapeutically useful acids, for example, hydrohalic acids, sulphuric acids, phosphoric acids, nitric acid or perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, such as formic, acetic, propionic, oxalic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, hydroxymaleic, dihydroxymaleic or pyroracemic acid; phenyl-acetic, benzoic, para-aminobenzoic, anthranilic, para-hydroxy benzoic, salicylic or para-aminosalicylic acid, methane sulphonic acid, ethane sulphonic acid, hydroxy-ethane sulphonic acid or ethylene-sulphonic acid; toluene sulphonic acids, naphthalene sulphonic acids or sulphanilic acid; methionine, tryptophane, lysine, arginine, cysteine or glutamic acid. Salts so obtained may be converted into the free bases, and the free bases may be converted into salts thereof.

The new pharmacologically useful compounds, their salts or quaternary ammonium compounds or corresponding mixtures can be used, for example, in the form of pharmaceutical preparations. These preparations contain the said compounds in admixture or conjunction with a pharmaceutical organic or inorganic carrier suitable for enteral or parenteral administration. As carriers there are used substances that do not react with the new compounds, for example, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, water, benzyl alcohols, gums, polyalkylene glycols, cholesterol or other known carriers for medicaments. The pharmaceutical preparations may be used, for example, in the form of tablets, dragées or in liquid form, such as solutions, suspensions or emulsions. If desired they may be sterilized and may contain auxiliary substances, such as preserving, stabilising, wetting or emulsifying agents. They may also contain therapeutically useful substances. The preparations are made up by the usual methods. They contain, for example, 1—100 mg, and advantageously 5—50 mg, of the active substance per dosage unit, and about 1 to 70%, advantageously 5 to 50%, of active substance.

When there are used in the process of the invention starting materials that are new they can be made by methods in themselves known or described herein.

As starting materials there are advantageously used in the process those which

lead to the especially valuable final products hereinbefore mentioned. The starting materials may also be used in the form of quaternary ammonium compounds or salts thereof. The 1-R<sub>1</sub>-3-R<sub>2</sub>-4-hydroxy-6-R<sub>3</sub>-pyrazolo - [3,4-d] - pyrimidines used as starting materials can be obtained by the process described in Specification No. 17102/61, (Serial No. 937722), Specification No. 17104/61 (Serial No. 937723) or Specification No. 17105/61 (Serial No. 937724) by reacting 2-R<sub>1</sub>-3-amino-4-carbethoxy-pyrazole with a nitrile of the formula R<sub>3</sub>CN with the use of sodium as condensing agent. In addition to the starting materials used in the Examples described below there may be used the following starting materials:

- 1 - methyl - 4 - hydroxy - 6 - (3<sup>1</sup>:4<sup>1</sup>:5<sup>1</sup> - trimethoxy - phenyl - methyl) - pyrazolo - [3,4-d]-pyrimidine, melting at 245°C; 85
- 1 - isopropyl - 4 - hydroxy - 6 - (3<sup>1</sup>:4<sup>1</sup>:5<sup>1</sup> - trimethoxy - phenyl - methyl) - pyrazolo - [3,4-d]-pyrimidine, melting at 195—196°C; 80
- 1 - isopropyl - 4 - hydroxy - 6 - para-ethoxybenzyl - pyrazolo - [3,4-d] - pyrimidine; melting at 175—176°C; 90
- 1 - cyclohexyl - 4 - hydroxy - 6 - benzylpyrazolo - [3,4-d] - pyrimidine, melting at 207—208°C; 95
- 1 - (3<sup>1</sup> - pentyl) - 4 - hydroxy - 6 - benzylpyrazolo - [3,4-d] - pyrimidine, melting at 144—145°C; 100
- 1 - cyclo - pentyl - 4 - hydroxy - 6 - benzylpyrazolo - [3,4-d] - pyrimidine, melting at 189—190°C; 105
- 1 - (β - hydroxy - ethyl) - 4 - hydroxy - 6 - benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 194—195°C; 110
- 1 - isopropyl - 4 - hydroxy - 6 - para - chlorbenzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 181—182°C; 115
- 1 - isopropyl - 4 - hydroxy - 6 - *m*-methoxybenzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 155—158°C; 120
- 1 - isopropyl - 4 - hydroxy - 6 - ethyl - pyrazolo - [3,4-d] - pyrimidine, melting at 180—182°C; 125
- 1 - [1<sup>1</sup> - ethoxy - butyl - (3<sup>1</sup>)] - 4 - hydroxy - 6 - benzyl - pyrazolo-[3,4-d] - pyrimidine, melting at 111—112°C; 130
- 1 - methyl - 4 - hydroxy - 6 - para - chlorbenzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 268—270°C; 130
- 1 - methyl - 4 - hydroxy - 6 - (2<sup>1</sup>:3<sup>1</sup> - di - methoxy - phenyl - methyl) - pyrazolo - [3,4-d] - pyrimidine, melting at 190—191°C.
- 1 - phenyl - 4 - hydroxy - 6 - *m* - methoxybenzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 235°C; 125
- 1 - α - pyridyl - 4 - hydroxy - 6 - benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 360°C; 130
- 4 - hydroxy - 6 - benzyl - pyrazolo-[3,4-d]-pyrimidine, melting at 290—292°C; 130

1 - isopropyl - 4 - hydroxy - 6 - (2<sup>1</sup>-methyl-propyl) - pyrazolo - [3,4-d] - pyrimidine, melting at 114—116°C;

5 1 - isopropyl - 4 - hydroxy - 6 - ortho - methoxy - benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 157—159°C;

10 1 - isopropyl - 4 - hydroxy - 6 - (2<sup>1</sup>-methyl-3<sup>1</sup> - methoxy - phenyl - methyl)-pyrazolo-[3,4-d] - pyrimidine, melting at 150—151°C;

1 - [3<sup>1</sup> - methyl - butyl - (2<sup>1</sup>)] - 4 - hydroxy-6 - benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 157—158°C;

15 1 - isopropyl - 4 - hydroxy - 6 - para - nitro-benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 196—198°C;

1 - isopropyl - 4 - hydroxy - 6 - para-amino-benzyl - pyrazolo - [3,4-d] - pyrimidine, melting at 211—212°C;

20 1 - sec.-butyl - 4 - hydroxy - 6 - isopropyl-pyrazolo - [3:4-d] - pyrimidine, melting at 146—148°C;

25 1 - sec.-butyl - 4 - hydroxy - 6 - (2<sup>1</sup>-methyl-propyl) - pyrazolo - [3:4-d] - pyrimidine, melting at 115—116°C;

The following Examples illustrate the invention. In the Examples the method of representing the structure of the pyrazolo-[3:4-d]-pyrimidines used as starting material has been chosen which shows the greatest number of nuclear double bonds.

#### EXAMPLE 1:

1.95 cc of dimethyl sulphate are added to a solution of 5.4 grams of 1-isopropyl-4-hydroxy-6-benzylpyrazolo [3:4-d]-pyrimidine in 30 cc of 1N-sodium hydroxide solution and the mixture is stirred for 1 hour at room temperature. The alkaline solution is thereupon extracted with ether and the ether residue is crystallized from petroleum ether. In this way, 1 - isopropyl - 5 - methyl - 6 - benzyl - 4 - oxo - 4:5 - dihydropyrazolo [3:4-d]-pyrimidine is obtained in colourless crystals having a melting point of 96—97°C.

The starting material may be obtained as described in our Specification No. 17102/61 (Serial No. 937724).

#### EXAMPLE 2:

50 A solution of 1.15 grams of sodium in 40 cc of absolute alcohol is added to 14.1 grams of 1 sec. butyl - 4 - hydroxy-6-benzyl-pyrazolo [3:4-d] pyrimidine in 60 cc of absolute alcohol and the mixture is boiled for 4 hours under reflux after adding 7.5 grams of diethylaminoethyl chloride. After cooling, the precipitated crystals are filtered off with suction, the filtrate is concentrated, 50 cc of 1N-hydrochloric acid are added to the residue and a little undissolved material is filtered off. The filtrate is adjusted to pH value of 10 with 2N-sodium hydroxide solution and extracted with ether. The oil obtained from the other residue is dissolved in 30 cc of absolute alcohol and 28.4 cc of

1.49 N-alcoholic hydrochloric acid are added to the solution. 1 - sec.-butyl-5-(β-diethyl-aminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydropyrazolo [3:4-d] pyrimidine is obtained as residue from the concentrated reaction solution in the form of the hydrochloride, which has a melting point of 147—148°C.

The 1 - sec.-butyl - 4 - hydroxy-6-benzyl-pyrazolo - [3:4-d] - pyrimidine employed as starting material can be obtained as described in our Specification No. 17105/61 (Serial No. 937724).

#### EXAMPLE 3:

13.4 grams of 1 - isopropyl-4-hydroxy-6-benzyl - pyrazolo - [3:4-d] - pyrimidine are added to a sodium ethylate solution, prepared from 1.2 grams of sodium and 300 cc of alcohol free from water. To form the sodium salt, stirring is carried out for 1 hour at room temperature. 5.5 grams of β-dimethylamino-ethyl chloride are added, the mixture is heated for 4 hours to boiling point and then evaporated to dryness *in vacuo*, the residue is dissolved in 100 cc of 1-N-hydrochloric acid, the solution is adjusted to a pH value of 10 with sodium hydroxide solution and the precipitated oil is absorbed in ether. The ether residue is recrystallized from petroleum ether. In this way, 1 - isopropyl - 5 - (β - dimethylaminoethyl) - 6 - benzyl-4-oxo-4:5 - dihydropyrazolo - [3:4-d] - pyrimidine is obtained in colourless crystals having a melting point from 115—117°C. The hydrochloride melts from 229—231°C.

#### EXAMPLE 4:

13.4 grams of 1 - isopropyl - 4 - hydroxy-6 - benzylpyrazolo - [3:4-d] - pyrimidine are added to a sodium ethylate solution, prepared from 1.2 grams of sodium and 300 cc of alcohol free from water. To form the sodium salt, stirring is carried out for 1 hour at room temperature. 7 grams of β-diethyl-aminoethyl chloride are added, mixture is heated for 4 hours to boiling point and then evaporated to dryness *in vacuo*, the residue is dissolved in 100 cc of 1N-hydrochloric acid, the solution is adjusted to a pH value of 10 with sodium hydroxide solution and the precipitated oil is absorbed in ether. Alcoholic hydrochloric acid is added to the ether residue. This is evaporated and the residue is recrystallized from ethyl acetate. In this way, the hydrochloride of 1-isopropyl-5-(β - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydropyrazolo[3,4-d] - pyrimidine is obtained in colourless crystals having a melting point of 202—203°C.

#### EXAMPLE 5:

13.4 grams of 1 - isopropyl - 4 - hydroxy-6 - benzyl - pyrazolo - [3,4-d]pyrimidine are added to a sodium ethylate solution, prepared from 1.2 grams of sodium and 300 cc of alcohol free from water. To form the sodium salt, stirring is carried out for 1 hour at 1.

room temperature. 8 grams of  $\gamma$ -diethylaminopropyl chloride are then added, the mixture is heated for 4 hours to boiling point and then evaporated to dryness *in vacuo*, the residue is dissolved in 100 cc of 1N-hydrochloric acid, the solution is adjusted to a pH value of 10 with sodium hydroxide solution and the precipitate oil is absorbed in ether. The ether residue is recrystallized from petroleum ether. In this way, 1-isopropyl - 5 - ( $\gamma$  - diethylaminopropyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydropyrazolo-[3:4-d] pyrimidine is obtained in colourless crystals having a melting point of 70—71° C. The hydrochloride melts at 173—175° C.

#### EXAMPLE 6:

1.2 grams of sodium in 25 cc of ethanol are added to 12 grams of 1-methyl-4-hydroxy-6-benzyl-pyrazolo - [3:4-d] - pyrimidine in 75 cc of alcohol. The mixture is boiled for 1 hour under reflux and 6 grams of  $\beta$  - diethylaminoethylchloride are thereupon added, whereupon heating is carried out for a further 3 hours to boiling point. The sodium chloride precipitated is filtered off, the filtrate is concentrated and the residue is crystallized from cyclohexane. 1-methyl-5-( $\beta$  - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo - [3:4-d]-pyrimidine is obtained in crystals having a melting point of 83—85° C. The hydrochloride melts at 219° C.

The 1 - methyl - 4 - hydroxy - 6 - benzyl-pyrazolo - [3:4-d] - pyrimidine employed as starting material can be obtained as described in our Specification No. 17105/61 (Serial No. 937724).

#### EXAMPLE 7:

A solution of 800 mg of sodium in 10 cc of ethanol is added to a suspension of 10 grams of 1 - phenyl - 6 - benzyl - 4 - hydroxypyrazolo - [3:4-d] - pyrimidine in 100 cc of ethanol and the mixture is boiled for 30 minutes under reflux. 5 grams of  $\beta$  - diethylaminoethyl - chloride in 10 cc of alcohol are thereupon added and boiling is continued for a further 3 hours. The sodium chloride precipitated is filtered off and the filtrate is evaporated to dryness *in vacuo*. The solid residue is recrystallized from cyclohexane-petroleum ether and in this way 1 - phenyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydropyrazolo-[3:4-d]-pyrimidine is obtained in crystals having a melting point of 103—105° C. The hydrochloride melts at 225° C.

The 1 - phenyl - 6 - benzyl - 4 - hydroxy-pyrazolo - [3:4-d] pyrimidine employed as starting material is obtained as described in our Specification No. 17105/61 (Serial No. 937724).

#### EXAMPLE 8:

9.1 grams of 1 - isopropyl - 4 - hydroxy-6 - methylpyrazolo - [3:4-d] - pyrimidine are added to a sodium ethylate solution pre-

pared from 1.2 grams of sodium and 150 cc of ethanol free from water. To form the sodium salt, stirring is carried out for 1 hour at room temperature. 7 grams of  $\beta$ -diethylaminoethyl chloride are added, the mixture is heated for 4 hours to boiling point and then evaporated to dryness *in vacuo*, the residue is dissolved in 100 cc of 1N-hydrochloric acid, the solution is adjusted to a pH value of 10 with sodium hydroxide solution and the precipitated oil is absorbed in ether. Alcoholic hydrochloric acid is added to the ether residue. The solvent evaporated and the residue is recrystallized from ethyl acetate. In this way, the hydrochloride of 1 - isopropyl - 5 - ( $\beta$  - di - ethylaminoethyl) - 6 - methyl - 4 - oxo - 4:5 - dihydropyrazolo-[3:4-d]-pyrimidine is obtained.

The 1 - isopropyl - 4 - hydroxy-6-methyl-pyrazolo[3:4-d] - pyrimidine employed as starting material is obtained as described in our Specification No. 17104/61 (Serial No. 937723).

#### EXAMPLE 9:

6.3 grams of dimethyl sulphate are added to a solution of 11 grams of 1:6-diisopropyl-4 - hydroxypyrazolo - [3:4-d] - pyrimidine in 75 cc of 2N-sodium hydroxide solution and stirring is carried out for 2 hours at room temperature and the mixture is allowed to stand overnight. The deposited precipitate is thereupon filtered off with suction and crystallized from petroleum ether. In this way, 1,6 - diisopropyl - 5 - methyl - 4 - oxo - 4:5 - dihydropyrazolo - [3:4-d] - pyrimidine is obtained in colourless crystals having a melting point of 75—77° C.

The 1:6 - diisopropyl - 4 - hydroxy - pyrazolo - [3:4-d] - pyrimidine employed as starting material is obtained as described in our Specification No. 17104/61 (Serial No. 937723).

#### EXAMPLE 10:

10 grams of 1:6 - diisopropyl-4-hydroxy-pyrazolo-[3:4-d]-pyrimidine are added to a sodium ethylate solution prepared from 1.05 grams of sodium and 150 cc of ethanol. To form the sodium salt, stirring is carried out for 1 hour at room temperature. 6.5 grams of  $\beta$  - diethylaminoethyl-chloride are added, the mixture is heated for 4 hours to boiling point and then evaporated to dryness *in vacuo*, the residue is dissolved in 100 cc of 1N-hydrochloric acid, the pH value adjusted to 10 with sodium hydroxide solution and the precipitated oil is absorbed in ether. The ether residue is distilled. 1:6-diisopropyl-5-( $\beta$  - diethylaminoethyl) - 4 - oxo - 4:5 - dihydro - pyrazolo - [3:4-d] - pyrimidine passes over at 138—140° C. at a pressure of 0.05 mm Hg.

#### EXAMPLE 11:

5.2 grams of 1 - isopropyl - 4 - hydroxy-6 - diphenylmethylpyrazolo - [3:4-d] - pyrimidine are added to a sodium ethylate solu-

tion prepared from 0.35 gram of sodium and 150 cc of ethanol. To form the sodium salt, stirring is carried out for 1 hour at room temperature. 2.1 grams of  $\beta$ -diethylaminoethyl chloride are added, the mixture is heated for 4 hours to boiling point and evaporated to dryness *in vacuo* and the residue is crystallized from petroleum ether. In this way, 1 - isopropyl - 6 - diphenylmethyl - 5 - ( $\beta$  - diethylaminoethyl) - 4 - oxo - 4:5 - dihydropyrazolo - [3:4-d] - pyrimidine is obtained in colourless crystals having a melting point of 124—125° C.

The 1 - isopropyl - 4 - hydroxy - 6 - diphenylmethylpyrazolo - [3:4-d] - pyrimidine employed as starting material is obtained as described in our Specification No. 17105/61 (Serial No. 937724).

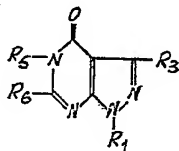
#### EXAMPLE 12:

1 - sec.-butyl - 5 - ( $\beta$  - diethylaminoethyl) - 4 - oxo - 4:5 - dihydro - 6 - benzyl-pyrazolo-[3:4-d]-pyrimidine is worked in conventional manner into tablets of the following composition:

1-sec.-butyl-5-( $\beta$ -diethylaminocethyl)-4-oxo-4:5-dihydro-6-benzyl-pyrazolo-[3:4-d]-pyrimidine	10 mg
lactose	35 mg
non-swellable starch	20 mg
wheat starch	10 mg
silicon dioxide	10 mg
arrowroot	12 mg
magnesium stearate	0.5 mg
talc	6 mg

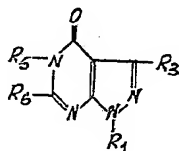
#### WHAT WE CLAIM IS:—

1. A compound of the general formula



in which  $R_1$  represents a hydrogen atom or an alkyl, hydroxy-alkyl, oxa-alkyl or cyclo-alkyl group, or an at most binuclear aryl group or a pyridyl group,  $R_3$  represents a hydrogen atom or a lower alkyl group,  $R_5$  represents an alkyl or tertiary aminoalkyl group, and  $R_6$  represents an alkyl or aralkyl group.

2. A compound of the general formula



in which  $R_1$  represents a hydrogen atom or a lower alkyl, cycloalkyl, hydroxy-lower-alkyl or oxa-lower-alkyl group, or an unsubstituted aryl group or a mono-, di- or tri-substituted aryl group substituted by halogen, alkoxy, alkyl, methylene-dioxy or trifluoromethyl, or represents a pyridyl group,  $R_3$  represents a hydrogen atom or a lower alkyl group,  $R_5$  represents a lower alkyl or a tertiary amino lower alkyl group, and  $R_6$  represents a lower alkyl group or an unsubstituted or substituted aralkyl group.

3. A compound of the general formula given in claim 1, in which  $R_1$  and  $R_3$  each represents a hydrogen atom or a lower alkyl group,  $R_5$  represents a di-lower-alkylamino-, pyrrolidino-, piperidino-, morpholino- or piperazino-lower-alkyl group, and  $R_6$  represents an unsubstituted benzyl group or a mono-, di- or trisubstituted benzyl group substituted in the phenyl group by chlorine, methoxy, methylene-dioxy, methyl or trifluoromethyl.

4. A physiologically tolerable quaternary ammonium compound of a compound claimed in any one of claims 1 to 3.

5. A physiologically tolerable salt of a compound claimed in any one of claims 1 to 3.

6. 1 - Secondary - butyl - 5 - ( $\beta$ -diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

7. 1 - Isopropyl - 5 - methyl - 6 - benzyl - 4 - oxo - 4:5 - dihydro - pyrazolo[3,4-d]-pyrimidine.

8. 1 - Isopropyl - 5 - ( $\beta$  - dimethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

9. 1 - Isopropyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

10. 1 - Isopropyl - 5 - ( $\gamma$  - diethylamino-propyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

11. 1 - Methyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

12. 1 - Phenyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - benzyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

13. 1 - Isopropyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - methyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

14. 1:6 - Di - isopropyl - 5 - methyl - 4 - oxo - 4:5 - dihydro - pyrazolo[3,4-d]-pyrimidine.

15. 1:6 - Di - isopropyl - 5 - ( $\beta$ -diethylaminoethyl) - 4 - oxo - 4:5 - dihydro - pyrazolo[3,4-d]pyrimidine.

16. 1 - Isopropyl - 5 - ( $\beta$  - diethylaminoethyl) - 6 - diphenylmethyl - 4 - oxo - 4:5 - dihydro-pyrazolo[3,4-d]pyrimidine.

17. A physiologically tolerable salt of any one of the compounds claimed in claims 6 to 13, 15 and 16.

18. The hydrochloride of any one of the compounds claimed in claims 6 to 13, 15 and 16.
- 5 19. A compound as claimed in claim 1 and described in any one of the Examples 1 to 11 herein.
- 10 20. A process for the manufacture of a pyrazolo[3,4-d]pyrimidine as claimed in claim 1 or a physiologically tolerable quaternary ammonium compound or a salt thereof, wherein the tautomerisable hydrogen atom in a 1-R<sub>1</sub>-3-R<sub>2</sub>-4-oxo-4,5-dihydro-6-R<sub>3</sub>-pyrazolo[3,4-d]pyrimidine is exchanged for the residue R<sub>4</sub> by reaction with a reactive ester of an alcohol of the formula R<sub>4</sub>-OH.
- 15 21. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 1 to 11 herein.
- 20 22. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 3 in admixture or conjunction with a pharmaceutically suitable carrier.
- 25 23. A pharmaceutical preparation which comprises a quaternary ammonium compound as claimed in claim 4 in admixture or conjunction with a pharmaceutically suitable carrier.
24. A pharmaceutical preparation which comprises a salt as claimed in claim 5 in admixture or conjunction with a pharmaceutically suitable carrier.
25. A pharmaceutical preparation which comprises the compound claimed in any one of claims 6 to 16 in admixture or conjunction with a pharmaceutically suitable carrier.
26. A pharmaceutical preparation which comprises a salt as claimed in claim 17 in admixture or conjunction with a pharmaceutically suitable carrier.
27. A pharmaceutical preparation which comprises a salt as claimed in claim 18 in admixture or conjunction with a pharmaceutically suitable carrier.
28. A tablet having substantially the composition given in Example 12 herein.
- 30
- 35
- 40
- 45

ABEL & IMRAY,  
Chartered Patent Agents,  
Quality House,  
Quality Court, Chancery Lane,  
London, W.C.2.